Proposed Decision Memo for Clinical Trial Policy (CAG-00071R)

Decision Summary

The Centers for Medicare & Medicaid Services (CMS) is proposing the following revisions to the Medicare National Clinical Trial Policy:

1) Rename the policy, the Clinical Research Policy (CRP).

2) Add a definition of research.

3) Continue the seven highly desirable characteristics and rename them “general standards for a scientifically and technically sound clinical research study” and add an additional standard: “The research study must have a written protocol.”

4) Revise the requirements that qualify a clinical study for Medicare coverage by renaming them “Medicare-specific standards,” eliminating the first, and combining and modifying the second and third requirements for greater clarity. Add the following Medicare-specific requirements:

- The research study must be registered on the ClinicalTrials.gov website prior to the enrollment of the first study subject.
- The research study protocol must specify and fulfill method and timing of public release of results.
- The research study must have explicitly discussed inclusion criteria and considered relevant subpopulations (as defined by age, gender, race/ethnicity, socioeconomic, or other factors) in the study protocol.
- The protocol must contain a discussion of how the results will generalize to the Medicare population.

5) The NCD process may establish additional standards through Coverage with Evidence Development (CED).

6) Rename routine costs to “routine clinical services” and clarify the definition.

7) Add a definition of administrative services required to carry out studies and clarify that Medicare will not cover administrative services.

8) Add a definition for investigational clinical services and cover those services when the service is available to Medicare beneficiaries that are not participating in a study or when it is required through CED.

9) Clarify those processes that ensure that both the Medicare-specific standards and the general standards for a scientifically and technically sound clinical research study are met.

- General standards:
  1. Studies approved by DHHS Agencies, the Veterans Administration or the Department of Defense.
  2. Studies approved by research centers or cooperative groups funded by one of the above Federal Agencies who have approved their process.
  3. Studies conducted under an Investigational New Drug (IND) where the protocol has been reviewed by the FDA.
  4. Studies that FDA requires and approves as a post-approval commitment.
  5. Studies required through CED.

- Medicare specific standards:
  CMS will use routine processes to ensure that the Medicare-specific standards are met.

10) Remove the following options for “deeming” studies:
- Self-certification process.
- IND Exempt studies.

These proposed changes are described in more detail below. The proposed NCD language is in Appendix A.

We are requesting public comments about this proposed determination pursuant to Section 731 of the Medicare Modernization Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

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Proposed Decision Memo

TO: Administrative File: CAG-0071R
Clinical Trial Policy

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SUBJECT: Proposed Decision Memorandum for Medicare National Clinical Trial Policy

DATE: April 10, 2007

I.Proposed Decision

The Centers for Medicare & Medicaid Services (CMS) is proposing the following revisions to the Medicare National Clinical Trial Policy:

1) Rename the policy, the Clinical Research Policy (CRP).

2) Add a definition of research.

3) Continue the seven highly desirable characteristics and rename them “general standards for a scientifically and technically sound clinical research study” and add an additional standard: “The research study must have a written protocol.”

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- The protocol must contain a discussion of how the results will generalize to the Medicare population.

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4. Studies that FDA requires and approves as a post-approval commitment.
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- Medicare specific standards:
  CMS will use routine processes to ensure that the Medicare-specific standards are met.

10) Remove the following options for “deeming” studies:

- Self-certification process.
- IND Exempt studies.

These proposed changes are described in more detail below. The proposed NCD language is in Appendix A.

We are requesting public comments about this proposed determination pursuant to Section 731 of the Medicare Modernization Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

II. Background

On September 19, 2000, the Health Care Financing Administration (now CMS) implemented a Clinical Trial Policy through the NCD process. The Clinical Trial Policy was developed in response to a June 7, 2000 Executive Memorandum, issued by President Clinton, requiring Medicare to pay for routine care costs in clinical trials.[1]

In the original NCD (NCD Manual 310.1 [printed in its entirety in Appendix B]), CMS, relying upon the authority of section 1862(a)(1)(E), determined the circumstances under which certain items and services would be reasonable and necessary when provided to Medicare beneficiaries in clinical trials. To be consistent with the requirements of section 1142 of the Act, CMS solicited the assistance of the Agency for Healthcare Research and Quality (AHRQ) in this endeavor. AHRQ recommended the standards and processes that would be most likely to ensure that the requirements of section 1142 of the Act would be met.

The current policy, unchanged since the original version in 2000, lists three requirements of a qualified clinical trial:

1) The subject or purpose of the trial must be the evaluation of an item or service that falls within a Medicare benefit category (e.g., physicians' service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids).

2) The trial must not be designed exclusively to test toxicity or disease pathophysiology. It must have therapeutic intent.

3) Trials of therapeutic interventions must enroll patients with diagnosed disease rather than healthy volunteers. Trials of diagnostic interventions may enroll healthy patients in order to have a proper control group.

It also defines seven highly desirable characteristics of a qualified trial:

1) The principal purpose of the trial is to test whether the intervention potentially improves the participants' health outcomes;

2) The trial is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use;

3) The trial does not unjustifiably duplicate existing studies;

4) The trial design is appropriate to answer the research question being asked in the trial;

5) The trial is sponsored by a credible organization or individual capable of executing the proposed trial successfully;

6) The trial is in compliance with Federal regulations relating to the protection of human subjects; and

7) All aspects of the trial are conducted according to the appropriate standards of scientific integrity.

After establishing these standards, the policy then discussed two options for qualifying trials as meeting these standards. The first option, a self-certification process, committed CMS to developing criteria that a trial's principal investigator could certify had been met by the trial. CMS did not implement this process.

Under the alternative option, clinical trials were deemed to be automatically qualified if they were:

1) Trials funded by NIH, CDC, AHRQ, HCFA, DOD, and VA;

2) Trials supported by centers or cooperative groups that are funded by the NIH, CDC, AHRQ, HCFA, DOD and VA;

3) Trials conducted under an Investigational New Drug application (IND) reviewed by the FDA; and

4) Drug trials that are exempt from having an IND under 21 CFR 312.2(b)(1) will be deemed automatically qualified until the qualifying criteria are developed and the certification process is in place. At that time the principal investigators of these trials must certify that the trials meet the qualifying criteria in order to maintain Medicare coverage of routine costs. This certification process will only affect the future status of the trial and will not be used to retroactively change the earlier deemed status.

Both options required the principal investigator of qualified trials to enroll those trials in a registry that CMS was to develop. That registry was not developed.

The current policy limits the payment for items and services provided to Medicare beneficiaries in qualified trials to routine costs. In general, the policy defines “routine costs” as those items and services that would generally be available to Medicare beneficiaries outside the trial. Among other things, it also excludes items and services that are the subject of the investigation even if they are covered outside the trial.

In the tracking sheet posted by CMS on July 10, 2006, the reconsideration of the Clinical Trial Policy NCD was announced. That tracking sheet referred to three overarching Agency goals for the policy:

1) Allow Medicare beneficiaries to participate in research studies;

2) Encourage the conduct of research studies that add to the knowledge base about the efficient, appropriate, effective, and cost-effective use of products and technologies in the Medicare population, thus improving the quality of care that Medicare beneficiaries receive; and,

3) Allow Medicare beneficiaries to receive care that may have a health benefit, but for which evidence for the effectiveness of the treatment or service is insufficient to allow for full, unrestricted coverage.

In an attempt to meet these goals, CMS proposed to address several issues:

- Clarify payment criteria for clinical costs in research studies other than clinical trials;
- Devise a strategy to ensure that Medicare covered clinical studies are enrolled in the NIH clinical trials registry website;
- Develop criteria to assure that any Medicare covered clinical research study include a representative sample of Medicare beneficiaries by demographic and clinical characteristics;
- Clarify the definitions of routine clinical care costs and investigational costs in clinical research studies including clinical trials;
- Remove the self-certification process that was never implemented;
- Clarify the scientific and technical roles of Federal Agencies in overseeing IND Exempt trials;
- Determine if coverage of routine clinical care costs is warranted for studies beyond those covered by the current policy;
- Clarify how items/services that do not meet the requirements of 1862(a)(1)(A) but are of potential benefit can be covered in clinical research studies as an outcome of the NCD process;
- Clarify whether and under what conditions an item/service non-covered nationally may be covered in the context of clinical research to elucidate the impact of the item or service on health outcomes in Medicare beneficiaries; and
- Discuss Medicare policy for payment of Humanitarian Use Device (HUD) costs.

CMS received public comments for 30 days after the tracking sheet was posted. CMS also convened a Medicare Evidence Development & Coverage Advisory Committee (MedCAC) to obtain public input and provide recommendations to CMS. Finally, CMS asked AHRQ to provide recommended changes using the input from the MedCAC as to whether the changes were consistent with section 1142 of the Act.

Additional Background

Section 520(m) of the Food, Drug, and Cosmetic Act (FDC Act), 21 U.S.C. § 360j, creates the Humanitarian Device Exemption (HDE) for humanitarian use devices. FDA's regulations define a Humanitarian Use Device (HUD) as a "medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year," 21 C.F.R. § 814.3(n). Approval of an HDE exempts such devices from the effectiveness requirements of sections 514 and 515 of the FDC Act. To receive an HDE, the sponsor of the HDE application must demonstrate that the HUD is safe and has probable benefit. CMS has no national policy concerning the coverage of HUDs with an HDE.

III. Authority

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under Title XVIII of the Social Security Act section1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, must not be otherwise excluded from coverage, and must be reasonable and necessary as defined in section1862(a)(1)(A).

Section 1862(a)(1)(A) states:

Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—which, except for items and services described in a succeeding subparagraph, are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member…

One of the succeeding subparagraphs to section 1862(a), section1862(a)(1)(E) of the Act states:

Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section…

Section 1142 in pertinent parts provides:

(a)(1) IN GENERAL.—The Secretary, acting through the Administrator for Health Care Policy and Research[2], shall—
(A) conduct and support research with respect to the outcomes, effectiveness, and appropriateness of health care services and procedures in order to identify the manner in which diseases, disorders, and other health conditions can most effectively and appropriately be prevented, diagnosed, treated, and managed clinically;

* * *

(2) EVALUATIONS OF ALTERNATIVE SERVICES AND PROCEDURES.—In carrying out paragraph (1), the Secretary shall conduct or support evaluations of the comparative effects, on health and functional capacity, of alternative services and procedures utilized in preventing, diagnosing, treating, and clinically managing diseases, disorders, and other health conditions.

* * *

(b) PRIORITIES. (1) IN GENERAL.—The Secretary shall establish priorities with respect to the diseases, disorders, and other health conditions for which research and evaluations are to be conducted or supported under subsection (a). In establishing such priorities, the Secretary shall, with respect to a disease, disorder, or other health condition, consider the extent to which—
(A) improved methods of prevention, diagnosis, treatment, and clinical management can benefit a significant number of individuals;
(B) there is significant variation among physicians in the particular services and procedures utilized in making diagnoses and providing treatments or there is significant variation in the outcomes of health care services or procedures due to different patterns of diagnosis or treatment;
(C) the services and procedures utilized for diagnosis and treatment result in relatively substantial expenditures; and
(D) the data necessary for such evaluations are readily available or can readily be developed.
(2) PRELIMINARY ASSESSMENTS.—For the purpose of establishing priorities under paragraph (1), the Secretary may, with respect to services and procedures utilized in preventing, diagnosing, treating, and clinically managing diseases, disorders, and other health conditions, conduct or support assessments of the extent to which—
(A) rates of utilization vary among similar populations for particular diseases, disorders, and other health conditions;
(B) uncertainties exist on the effect of utilizing a particular service or procedure; or
(C) inappropriate services and procedures are provided.

(3) RELATIONSHIP WITH MEDICARE PROGRAM.—In establishing priorities under paragraph (1) for research and evaluation, and under section 914(a) of the Public Health Service Act for the agenda under such section, the Secretary shall assure that such priorities appropriately reflect the needs and priorities of the program under title XVIII, as set forth by the Administrator of the Centers for Medicare & Medicaid Services.

IV. Discussion with Review of Comments and MedCAC and AHRQ input

During the initial 30-day public comment period, CMS received public comments from 53 different groups and individuals. Seven comments originated from academic health centers; 11 from the medical device and pharmaceutical industry; 20 from professional societies and interest groups; and 15 from individual physicians, nurses, and members of the medical billing, compliance, and consulting communities. Nearly every commenter voiced support for CMS' intention to revise its current Clinical Trial Policy.

On December 13, 2006, CMS convened a meeting of the MedCAC to solicit recommendations for the Clinical Trial Policy reconsideration. The presentations, minutes, and transcript of that meeting are available on the CMS coverage website.

On January 24, 2007, AHRQ convened a Federal Panel meeting to discuss revisions to the Clinical Trial Policy. The purpose of the Federal Panel meeting was to establish those circumstances under which AHRQ would be comfortable that a study was conducted pursuant to section 1142 of the Act.

In this section, we will discuss the Agency's proposed changes to the current Clinical Trial Policy as a result of recommendations from both the MedCAC and AHRQ and our consideration of public comments on the issues raised in the tracking sheet that opened the policy for reconsideration.

The Clinical Trial Policy currently addresses several major categories of issues:

- General issues.
- Appropriate standards of a clinical trial that, if met, would ensure that the study is conducted pursuant to section 1142 of the Act.
- Appropriate processes that ensure that those standards are met.
- Items and services that are covered in studies meeting those standards.

A. GENERAL ISSUES

1. Reconsideration

a. Public Comments

Overall, commenters expressed support for CMS' intention to revisit our 2000 Clinical Trial Policy. Commenters were pleased that CMS recognized the numerous challenges that the healthcare community has experienced in implementing this decision, and that the Agency remains committed to preserving the goals of President Clinton's 2000 executive memorandum—ensuring that seniors receive timely access to appropriate medical technologies by encouraging their voluntary participation in clinical trials.

Nearly all commenters cautioned CMS against using this reconsideration as an opportunity to restrict the coverage currently available to beneficiaries.

b. MedCAC Recommendations

No comments.

c. AHRQ Recommendations

No comments.

d. Discussion

We share the commenters' concerns that the current Clinical Trial Policy presents administrative challenges, which could potentially restrict beneficiaries' access to study participation, and agree that policy changes should be directed at removing these barriers.

2. Name change

CMS suggested that the name of the policy be changed to the Clinical Research Policy (CRP). Many researchers have a very narrow definition of "clinical trial" and as such many studies that CMS would like to support may not be included. By proposing a change to the name of the policy to the CRP, we hope to signal our continued support of beneficiaries' participation in the full range of qualified, scientifically sound research projects.

a. Public Comments

Several individuals remarked that changing the name of the Clinical Trial Policy to the Clinical Research Policy would be indicative of CMS' commitment to funding the routine costs of different types of studies such as observational studies, registries, and natural history studies—for which commenters voiced support.

Commenters remarked that as CMS extends coverage to new types of research studies, the Agency should take a leadership role in encouraging the development of quality criteria (i.e., the characteristics of a robust registry). Some commenters also mentioned that CMS should work with other DHHS stakeholders in developing detailed guidance about protecting patient privacy in disseminating registry data.

b. MedCAC Recommendations

The MedCAC agreed with the name change to Clinical Research Policy.

c. AHRQ Recommendations

AHRQ did not comment on the name change.

d. Discussion

CMS agrees that the conventional definition of clinical trial fails to capture the scope of opportunities available to Medicare beneficiaries in clinical study participation. By proposing a change to the name of the policy to the CRP, we hope to signal our continued support of beneficiaries' participation in the full range of qualified, scientifically sound research projects. CMS also agrees that working with its Federal partner agencies, such as AHRQ, to encourage the development of advances in research methodologies is a good idea. As an example, CMS has worked with AHRQ, through AHRQ's Effective Healthcare Program, to produce a reference for the design and use of successful registries. More information about this project is available on AHRQ's website at http://effectivehealthcare.ahrq.gov/decide/registryOutline.cfm. CMS proposes to change the title of this policy to the:

Clinical Research Policy

3. <u>Definition of research</u>

The MedCAC noted that CMS did not define research in the current Clinical Trial Policy and should do that separately from defining the standards of a good trial.

a. Public Comments

None received.

b. MedCAC Recommendations

The MedCAC recommended the adoption of the following definition of clinical research:

Clinical research is the observation of events in groups of individuals who share a particular characteristic, such as a symptom, sign, or illness; or a treatment or diagnostic test provided for the symptom, sign, or illness. Inferences are made based upon comparisons of rates of predefined outcomes among groups. Procedures are in place to assure that the rights, safety, and wellbeing of study participants are protected. Examples include: studies of diagnostic tests; primary & secondary prevention studies; health services research; and studies of comparative effectiveness.

c. AHRQ Recommendations

AHRQ recommended the following general definition of a clinical research:

Clinical research is the observation of events in groups of individuals who share a particular characteristic, such as a symptom or illness; or who have the same treatment or diagnostic test provided for a symptom or illness. Inferences are made based on comparisons of predefined health outcomes among groups. Procedures are in place to assure that the rights, safety, and wellbeing of research study participants are protected. Research studies need to conform to all applicable Federal regulations concerning human subject protection and privacy including 45 C.F.R. Part 46 and Parts 160 and 164.

Some examples of the types of clinical studies that might be supported follow, but this list should not be considered an all-inclusive list:

- Randomized controlled trials and other comparative clinical studies of effectiveness and comparative effectiveness;
- Observational clinical studies of outcomes of specific interventions, primary and secondary prevention strategies, or of implemented strategies related to delivery of care or testing of hypotheses regarding health services research ;
- Clinical studies of diagnostic tests, including measurements of sensitivity and specificity and impact on physician decision making and patient outcomes.

d. Discussion

We agree with the need for a definition of research in this policy as the MedCAC recommended. We believe that the AHRQ recommendation more clearly outlines both the definition and types of trials that fit under that definition and propose to include it in the policy.

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Some examples of the types of clinical studies that might be supported follow, but this list should not be considered an all-inclusive list:

- *Randomized controlled trials and other comparative clinical studies of effectiveness and comparative effectiveness;*
- *Observational clinical studies of outcomes of specific interventions, primary and secondary prevention strategies, or of implemented strategies related to delivery of care or testing of hypotheses regarding health services research; and*
- *Clinical studies of diagnostic tests, including measurements of sensitivity and specificity, and impact on physician decision making and patient outcomes.*

B. STANDARDS

The current Clinical Trial Policy has three requirements and seven highly desirable characteristics that a clinical trial must meet to qualify for Medicare coverage. The three requirements were specific Medicare standards that were components of the general standards encompassed in the seven highly desirable characteristics that Medicare believed most relevant to its population. They were not independent standards but subsets of the general study standards that CMS wanted to ensure were met in qualified trials. For instance, one Medicare specific requirement was for the study to have therapeutic intent. There are well-designed trials without therapeutic intent that meet the seven highly desirable characteristics. Thus, this specific standard, from within the general characteristics that Medicare wanted to ensure were met, was added to define Medicare's intentions for trial coverage.

CMS proposed to continue this dual set of standards. The first set includes general standards any good trial should meet. The second set includes particular aspects of the general standards that Medicare is particularly interested in ensuring are met.

CMS proposed that these standards be reclassified as:

- Scientifically and technically sound general study standards; and
- Medicare-specific standards.

Both the MedCAC and AHRQ agreed with this classification scheme. However, for clarity and format consistency, we believe that the Medicare-specific standard concerning CED belongs in a separate category. Based on these recommendations, we are proposing to modify the policy to reclassify the standards as:

- *General standards for a scientifically and technically sound clinical research study;*
- *Medicare-specific standards of a clinical research study; and*
- *National Coverage Determination Coverage with Evidence Development standards.*

1. General Standards for a Scientifically and Technically Sound Clinical Research Study

Seven highly desirable characteristics

The current policy lists seven highly desirable characteristics of a qualified trial. CMS requested input on the continued validity of these standards or if alternative or additional standards be adopted.

a) Public Comments

There were no substantive comments directed towards revising the seven highly desirable characteristics of a clinical study as written in the current NCD.

b) MedCAC Recommendations

The MedCAC considered the current list of seven desirable characteristics of a clinical study, and determined that they sufficiently define characteristics of a good clinical study and recommended that they be continued.

c) AHRQ Recommendations

AHRQ agreed that the current seven desirable characteristics of a clinical study continue to define a good clinical study and, with minor language changes, recommended CMS continue those in the current policy. Its recommended language is:

AHRQ will support research that meets the following general standards for a scientifically and technically sound clinical research study:

- The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes
- The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use
- The research study does not unjustifiably duplicate existing studies
- The research study design is appropriate to answer the research question being asked in the study
- The research study is sponsored by an organization or individual capable of executing the proposed study successfully
- The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 C.F.R. Part 46 and Parts 160 and 164. The studies have a data and safety monitoring plan.
- All aspects of the research study are conducted according to the appropriate standards of scientific integrity

d) Discussion

Both the MedCAC and AHRQ agreed that the current seven highly desirable characteristics are sufficient with minor modifications to ensure that the study is conducted pursuant to section 1142 of the Act. The modifications replace the word "trial" with "study" and add other minor modifications. We agree with the language changes recommended. We are adding some additional references for the standard that addresses human subject protection. The FDA has separate standards that apply to research that they oversee and we will add that language. We propose to adopt the following general standards for a scientifically and technically sound clinical research study:

AHRQ will support research that meet the following general standards a scientifically and technically sound clinical research study:

- *The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes;*
- *The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use;*
- *The research study does not unjustifiably duplicate existing studies;*
- *The research study design is appropriate to answer the research question being asked in the study;*
- *The research study is sponsored by an organization or individual capable of executing the proposed study successfully;*
- *The research study is in compliance with all Federal regulations relating to the protection of human subjects found at 45 C.F.R. Part 46. If the study is FDA-regulated, it also must be in compliance with 21 C.F.R. Parts 50 and 56; and*
- *All aspects of the research study are conducted according to the appropriate standards of scientific integrity.*

Written Protocol

While most studies are undertaken only after a detailed protocol has been developed, some are not. The protocol is the primary source of knowledge on the proposed design and management of the study. Without this document, reviewers and funders are unable to ascertain the quality and validity of the study. The exercise of committing to paper all the aspects of the study is crucial to ensuring that all potential concerns have been addressed.

a) Public Comments

Since this requirement was raised for the first time at the MedCAC meeting, the public was not asked to comment on this issue when the tracking sheet was released.

b) MedCAC Recommendations

The MedCAC recommended the addition of the following Medicare-specific requirement:

All studies must have a written protocol.

c) AHRQ Recommendations

AHRQ agreed with this concept and recommended some minor changes from the MedCAC language. AHRQ's recommended language is:

All research studies have a written protocol.

d) Discussion

While it is expected that all studies begin with a written protocol, the historical context provided at the MedCAC and supported by AHRQ convinces us that this requirement should be expressly stated. It is impossible to evaluate the adequacy of trial design without a written protocol. We do not propose to define the content of that protocol. Numerous Federal Agencies and other scientific entities have done that. However, we propose to add the following to the list of general standards:

All research studies have a written protocol

Summary

The recommendations above result in the following changes to the CRP:

AHRQ will support research that meets the following general standards for a scientifically and technically sound clinical research study:

1. *The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.*
2. *The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.*
3. *The research study does not unjustifiably duplicate existing studies.*

4. *The research study design is appropriate to answer the research question being asked in the study.*
5. *The research study is sponsored by an organization or individual capable of executing the proposed study successfully.*
6. *The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is FDA-regulated, it also must be in compliance with 21 CFR Parts 50 and 56.*
7. *All aspects of the research study are conducted according to the appropriate standards of scientific integrity.*
8. *All research studies have a written protocol.*

2. Medicare-Specific Standards

Most of the issues that concern CMS about the design and conduct of clinical research studies are encompassed in the general standards listed above. However, there are components of the general standards for a scientifically and technically sound clinical research study that are most relevant to CMS. Therefore, we want to ensure these are met and will assess them separately from the general standards. As discussed in the Approval section below, differing processes will be used to determine if these standards are met.

Benefit Category

The first requirement in the current policy relates to having a benefit category. This is not a standard for studies; rather it is a statutory requirement for coverage. We proposed moving that requirement to another section of the NCD and both the MedCAC and AHRQ agreed.

Therapeutic Intent

CMS proposed changes to the second and third requirements to clarify therapeutic intent. CMS wanted, in the current policy, to ensure that Medicare coverage was not provided for studies in which only basic safety or disease pathophysiology was being studied.

a) Public Comments

Several commenters remarked that the “therapeutic intent” requirement of the 2000 Clinical Trial Policy is too vague. Specifically, they remarked that studies would not necessarily have to include therapeutic intent as a primary objective (as stated in the study protocol) in order to confer therapeutic benefit for a patient; therefore, these studies should be considered to meet the “therapeutic intent” threshold. In fact, a few commenters suggested that therapeutic intent is implicit in any trial in phase II or later. Another commenter asked that CMS explicitly cover or non-cover phase I and prevention trials under this element of the policy.

Other commenters suggested that therapeutic intent can be demonstrated outside of the protocol objectives—for example, a trial can have therapeutic intent if it measures an endpoint that could have direct or indirect impact on the patient’s health. These commenters warned CMS against relying on “*mechanistic indicia*,” such as the phase of a trial or where an objective is listed in a protocol document. Rather CMS should rely on a variety of measures to make this indication—the outcomes measures, expectations of investigators and patients, physicians’ intentions in enrolling subjects, etc.

b) MedCAC Recommendations

The majority of members recommended that the second and third criteria read:

The study must not be designed primarily to test toxicity or disease pathophysiology. Phase I trials that have therapeutic intent as one of the objectives may meet the standard only if the disease is chronic, life threatening, or debilitating.

c) AHRQ Recommendations

AHRQ concurred with the MedCAC recommendation with some minor changes:

The research study must not be designed primarily to test toxicity or disease pathophysiology. Phase I trials that have therapeutic intent as one of the objectives may meet the CMS beneficiary protection standard only if the disease is chronic, life threatening, or debilitating.

d) Discussion

CMS understands that a broad definition of therapeutic intent recognizes the notion that many research projects could be considered to have varying degrees of contributions towards understanding those interventions that improve health outcomes for patient populations. We agree that in some cases, safety and toxicity trials may assess the benefits of the interventions they examine. However, we must balance this with an operating policy that is easily understood by the provider community and enforceable and reproducible across Medicare contractors.

As discussed above, the MedCAC and AHRQ recommended a single standard that included a discussion of Phase I trials as defined in FDA regulations at 21 C.F.R. 312.12. We are proposing to adapt and clarify the MedCAC and AHRQ recommendation and will add the following to the new policy:

The clinical research study is not designed to exclusively test toxicity or disease pathophysiology. Research studies, including some Phase I trials, whose protocols commit to measuring therapeutic outcomes as one of the objectives, may meet this standard only if the disease being studied is chronic, life threatening, or debilitating.

Trial Registration

The current policy stated that CMS would establish a registry of all covered trials. Although a registry was not established by CMS, we suggested that this requirement be continued in a modified form by requiring the NIH ClinicalTrials.gov website as the required registry. We recommended that this standard be added to the list of Medicare-specific standards.

a) Public Comments

Commenters pointed out that the NIH/National Library of Medicine clinical trials registry is only one of many sources for clinical trials information. As such, some commenters argued that other sites outside of the DHHS should be recognized as meeting this criterion of coverage.

Other commenters supported CMS' proposal, stating that other entities—such as the International Committee of Medical Journal Editors—already impose this requirement prior to accepting manuscripts of study results for publication.

Some commenters who were supportive of this idea made distinctions between different types of trials—several individuals remarked that registration should only be required for trials at Phase II and beyond (i.e., Phase I trials should not be required to register in all cases). One commenter sought clarification that all study types be added to the NIH website—for example, ClinicalTrials.gov supports the ability to register observational studies on the site.

Several commenters from the medical device and pharmaceutical manufacturing industries expressed concern that mandatory registration of upcoming clinical trials is contrary to competitive business practice, as this requirement would require trial sponsors to disclose potentially sensitive trade secrets to the public. These commenters urged that CMS criteria strike a balance between transparency and proprietary information by leaving this as a voluntary criterion.

b) MedCAC Recommendations

The MedCAC recommended the addition of the following to the Medicare-specific standards:

The study must be registered on the ClinicalTrials.gov website prior to the enrollment of the first study subject.

c) AHRQ Recommendations

AHRQ agreed with the MedCAC language, but recommended that this standard be included in the list of general study standards.

d) Discussion

Contemporaneously with the implementation of the 2000 Clinical Trial NCD, the National Institutes of Health/National Library of Medicine (NIH/NLM) established a clinical trials registry (ClinicalTrials.gov) to meet the requirement of the 1997 Food and Drug Administration Modernization Act. After a thorough review of the NIH/NLM ClinicalTrials.gov website, we believe that all studies covered under this policy should be registered in this registry prior to enrollment of the first subject. Many internationally and nationally recognized research organizations and peer-review publications have ratified the registration of clinical studies into the ClinicalTrials.gov registry. Registration into this registry assures that beneficiaries will have pertinent information about clinical research Medicare supports—an essential component of transparency to facilitate patient-provider informed decision-making. The World Health Organization and International Committee of Medical Journal Editors (WHO/ICMJE) data elements are the required data elements in this registry. Information about this registry may be obtained at http://www.clinicaltrials.gov/.

CMS recognizes the industry's sensitivity to disclosing study information—including study results—to the public through a national clinical trials registry. However, this sensitivity must be balanced against the public's desire to obtain information about the studies that their Medicare premiums and tax dollars support. Both the MedCAC and AHRQ agreed with this recommendation. AHRQ, however, believed that this requirement should be part of the general standards to ensure that approving agencies were cognizant of its importance. We believe that the general standards encompass this standard; but because of its relevance to the Medicare program, we prefer listing this requirement as a Medicare-specific standard to allow CMS to specifically review the adherence to this standard. We propose adding this requirement to the Medicare-specific standards. The proposed standard is:

The research study is registered on the ClinicalTrials.gov website prior to the enrollment of the first study subject.

Release of study results

The current policy does not discuss release of results from covered trials. CMS suggested that study protocols explicitly address plans for the dissemination of study results and findings and that this be added to the list of Medicare-specific standards.

a) Public Comments

Since this requirement was raised for the first time at the MedCAC meeting, the public was not asked to comment on this issue when the tracking sheet was released.

b) MedCAC Recommendations

The MedCAC recommended the addition of the following Medicare-specific requirement:

The study protocol must specify method and timing of public release of all pre-specified outcomes regardless of outcome or completion of trial.

c) AHRQ Recommendations

AHRQ agreed with this concept but again believed that this issue had such importance that it also needed to be added to the list of general standards for a scientifically and technically sound clinical research study. AHRQ also recommended some changes from the MedCAC language. AHRQ's recommended language is:

The research study protocol must specify and fulfill method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early.

d) Discussion

It is imperative that studies for which Medicare has made payment of any clinical costs be made available to the public regardless of the outcomes. We are aware that ClinicalTrials.gov does not have a mechanism for posting results at this time and that trial sponsors and the public depend on the medical literature for announcing their results. If trial results are not published they do not add to the clinical evidence base and cannot be used for medical decision-making. CMS will work with other government agencies and the research community to develop routine outlets for release of these results. Until that is completed, we are proposing that the results for all primary and secondary outcome measures must be made publicly available as the analyses are completed. These can be disseminated to the public in peer-reviewed publications or in suitable public web based databases. If and when a Federal government database of results becomes available, this would be considered preferable to a sponsor-supported database. For now, a sponsor-supported database would be considered acceptable if it clearly states the sponsor, the relationship of the sponsor to the items being studied, and the methods of scientific review of the results. Any sponsor-supported database must be made available to the public.

The MedCAC and AHRQ agreed with this concept and AHRQ recommended that it be added to the general standards list rather than the Medicare-specific standards list. We believe that the general standards of a scientifically and technically sound clinical research study encompass this standard: but because of its relevance to the Medicare program we prefer listing this requirement as a Medicare-specific standard to allow CMS to specifically review the adherence to this standard. We propose adding this requirement to the Medicare-specific standards. The proposed standard is:

The research study protocol specifies and fulfills method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early.

Health Disparities

Congress recognized the lack of representation of many subpopulations in many research studies in the NIH Revitalization Act of 1993.[3] The NIH implemented the statute in the *Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October, 2001.*[4]

In its tracking sheet, CMS asked the public to provide comment on the development criteria to assure that any Medicare covered clinical research study includes a representative sample of Medicare beneficiaries, by demographic and clinical characteristics.

a) Public Comments

In general, commenters were not supportive of this proposal. Commenters expressed concern that this requirement would be insurmountably challenging for CMS to implement and enforce, creating additional administrative burdens for well-intentioned providers. Several commenters agreed that the demographic characteristics of the study's participants should be driven by clinical considerations, rather than by a desire to mirror the universe of Medicare beneficiaries.

Some commenters also argued that this requirement would discourage the enrollment of Medicare beneficiaries in future trials—investigators may be unwilling or unable to meet this criterion, thus precluding participation of *any* beneficiaries and reducing access to new technology.

Commenters from throughout the healthcare community also expressed concern about preserving the scientific integrity of the protocol in the face of this requirement. A majority of commenters who addressed this topic stated that this requirement would affect study designs, particularly those of multi-site trials, whose investigators may experience geographic variation in their recruitment successes. A few commenters offered that NIH already takes steps to assure equitable access to trial participation, and that CMS' standard may counter this effort.

As an alternative, three commenters postulated that CMS should increase the visibility of clinical trials among the Medicare population, and remove administrative barriers for investigators to accept these patients into studies.

b) MedCAC Recommendations

CMS proposed more specific language to the MedCAC:

The study must have explicitly discussed consideration of relevant subpopulations (as defined by age, gender, race/ethnicity, or other factors) in the study protocol.

The MedCAC concurred with the recommended addition.

c) AHRQ Recommendations

Again, AHRQ concurred with the concept but recommended that it be added as a general standard for a scientifically and technically sound clinical research study. They also recommended some language revisions:

The research study must have explicitly discussed proposed inclusion criteria and considered relevant subpopulations (as defined by age, gender, race/ethnicity, socioeconomic or other factors) in the study protocol.

d) Discussion

CMS wants to support studies that allow Medicare beneficiaries to voluntarily participate in research studies and encourage the conduct of research studies that add to the knowledge base about the efficient, appropriate, effective, and cost-effective use of products and technologies in the Medicare population, thus improving the quality of care that Medicare beneficiaries receive. Well-designed studies have protocols that define the populations with the highest risk of having the disease or condition being studied. If data are not available that clearly demonstrate differences of clinical importance in subgroups defined by gender, race/ethnicity, age, or other relevant subpopulations, then the protocol must discuss the necessary steps to enroll sufficient numbers of these populations to ensure a valid analysis of the intervention effects.

CMS understands the commenters' concerns, but it is not our intention to require a specific enrollment of all subpopulations. It is, however, our intention that all covered study protocols address all populations affected by the technology under investigation with special emphasis on minority and other groups that have experienced disparities in health care due to a lack of quality research data. If convincing evidence indicates that no differences exist between identified subgroups, that information should be noted in the protocol. If that evidence does not exist, then the protocol must discuss how the study intends to address these issues. One option is to power the study to address outcomes in each subgroup separately. Alternatively, the study may choose to analyze the subgroups together and test for interaction. While not requiring any specific process, CMS expects that subgroup differences be defined and that protocols discuss how the study will evaluate any difference found.

With the support of the MedCAC and AHRQ, CMS recommends adoption of the language for this standard. As discussed above, listing this requirement as a Medicare-specific standard does not mean that it is not encompassed within the general standards. Adding it to this list allows CMS to specifically review the adherence to this standard. We propose adding this requirement to the Medicare-specific standards with minor clarifying language. The proposed standard is:

The research study protocol must have explicitly discussed inclusion criteria and considered relevant subpopulations (as defined by age, gender, race/ethnicity, socioeconomic or other factors).

Medicare Populations

In addition to the subpopulations addressed by the NIH, CMS serves a unique population—the elderly. We commonly review evidence that does not include this population. Therefore, we suggested that unless there are clear data documenting that no important differences exist between the Medicare elderly and the population studied, the study must enroll sufficient numbers of these populations to ensure that the analysis of the results of the intervention may be applicable to the Medicare population. This is especially important when the results are intended to be included in an external request to open a national coverage analysis.

a) Public Comments

In general, commenters were again not supportive of this proposal. Commenters cautioned that, should CMS continue to pursue this element of the policy, the Agency must delineate very clear guidelines about how this element could be implemented without affecting the access Medicare beneficiaries may already have to study participation.

b) MedCAC Recommendations

CMS provided specific language to the MedCAC:

If the study results are to be used to inform Medicare coverage policy, the study must contain an explicit discussion of how the enrollment process will ensure that sufficient Medicare populations are included to clinically and statistically determine that Medicare populations benefit from the intervention.

The MedCAC was uncomfortable with this language. Some MedCAC members stated that it was implicit and as such did not need to be part of the research policy. Others members agreed with some of our public commenters that requiring specific numbers of Medicare beneficiaries would make studies difficult to complete. The MedCAC recommended the following revision:

The protocol must contain a discussion of how the results will generalize to the Medicare population to infer whether Medicare patients benefit from the intervention and whether the results are generalizable to Medicare beneficiaries.

c) AHRQ Recommendations

AHRQ agreed with this concept. They reviewed the MedCAC recommendation and suggested the following changes:

The protocol must contain a discussion of how the results will generalize to the Medicare population to infer whether Medicare patients may benefit from the intervention. In particular, the protocol must describe the potential impact of age-specific and other factors on outcomes and whether the research study is powered sufficiently to draw conclusions with respect to the Medicare population.

d) Discussion

CMS understands the commenters' concerns. However, we expect that the results of all approved studies will specifically benefit the Medicare population and, as such, covered studies must address how the study will affect the Medicare elderly population if it desires to enroll and receive payment for services provided to Medicare beneficiaries within that study.

We agree that the MedCAC and AHRQ recommended language more clearly expresses our intent. Therefore, we propose to add this Medicare-specific standard to the new policy:

The research study protocol contains a discussion of how the results will generalize to the Medicare population to infer whether Medicare patients may benefit from the intervention. In particular, the protocol describes the potential impact of age-specific and other factors on outcomes and whether the research study is powered sufficiently to draw conclusions with respect to the Medicare population.

Summary

The recommendations above result in the following changes to the Medicare-specific standards in the CRP:

1) The clinical research study is not designed to exclusively test toxicity or disease pathophysiology. Research studies, including some Phase I trials, whose protocols commit to measuring therapeutic outcomes as one of the objectives, may meet this standard only if the disease being studied is chronic, life threatening, or debilitating.
2) The research study is registered on the ClinicalTrials.gov website prior to the enrollment of the first study subject.
3) The research study protocol specifies and fulfills method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early.
4) The research study protocol must have explicitly discussed inclusion criteria and considered relevant subpopulations (as defined by age, gender, race/ethnicity, socioeconomic or other factors).
5.) The research study protocol contains a discussion of how the results will generalize to the Medicare population to infer whether Medicare patients may benefit from the intervention. In particular, the protocol describes the potential impact of age-specific and other factors on outcomes and whether the research study is powered sufficiently to draw conclusions with respect to the Medicare population.

3. National Coverage Determination (NCD) Coverage with Evidence Development (CED) Standard

In July 2006, the Agency posted guidelines entitled, “National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development.” If, in an NCD, CMS determines that a technology is only covered when used within a research study, the NCD will define the additional required standards that such a required study must meet. These would then be specific standards that CMS would want to ensure were met in addition to the general standards and the Medicare specific-standards.

a) Public Comments

The commenters addressing CED were all supportive of adding this to the new clinical research policy.

b) MedCAC Recommendations

The MedCAC agreed that additional standards be defined through the NCD process.

c) AHRQ Recommendations

AHRQ believes that CED is an important tool to ensure that particular research appropriately reflects the needs and priorities of the Medicare program.

d) Discussion

CMS agrees with MedCAC and AHRQ recommendations, and proposes to add the following to the new policy.

CMS may require additional Medicare-specific standards for clinical research studies that have been identified through the NCD process using CED.

C. APPROVAL PROCESSES

The current Clinical Trial Policy outlines two options for ensuring that covered trials meet the general standards outlined in the policy—deeming and self-certification. We propose to collapse all processes under the heading “Approval Processes.”

1. Current “Deemed” Processes

In the original clinical trial policy, AHRQ wanted to ensure that any approval process would be sufficient to ensure that covered trials were conducted pursuant to section 1142 of the Act. One option determined that the processes used by other Federal Agencies who routinely reviewed and/or funded trials were sufficient to meet this requirement. Thus, the clinical trial policy currently “deems” that the broadly defined characteristics of a clinical trial have been met if funded or supported by centers or cooperative groups that are funded by the NIH, CDC, AHRQ, HCFA, DOD, and VA, conducted under an IND application reviewed by the FDA, or are studies of IND exempt drugs.

Trials Funded by NIH, CDC, AHRQ, HCFA, DOD, and VA

CMS initially recommended that the first process be maintained but expanded to all Federal Agencies.

a) Public Comments

Commenters generally agreed with continuing this process but did not comment on the expansion to all Federal Agencies.

b) MedCAC Recommendations

The MedCAC reviewed this current process for ensuring that covered clinical research studies meet the standards outlined in this policy. They made the following recommendation:

A study is deemed to have met the scientifically and technically sound general study standards if:

- The study is reviewed, approved, and funded by a Federal Agency.

c) AHRQ Recommendations

AHRQ was supportive of studies that have successfully passed through processes that include individual protocol review because the validity of a research study is ultimately determined by specific details in the individual study protocol. AHRQ believes that the crucial factor in trial approval is that a thorough review of the protocol be performed by competent entities prior to CMS approval of that study. AHRQ agreed with MedCAC that, in general, the processes used by the Federal Agencies listed will ensure that the research studies will be safe and scientifically sound and thus meet the general standards for a scientifically and technically sound clinical research study. AHRQ did recommend that the expansion from the previous list to all Federal Agencies be narrowed to only include those within the Department of Health and Human Services (DHHS) as well as the VA and DOD who were previously included. AHRQ was unfamiliar with the types of clinical research that might be performed by other Departments and the extent to which those Departments would review the protocols. AHRQ recommended the following language:

The following processes will assure that the standards of scientifically and technically sound and safe research are met and assure that the research is conducted with AHRQ support pursuant to section 1142 of the Act:

Studies of health outcomes reviewed and funded by a program component of DHHS, the Veterans Administration, or the Department of Defense.

d) Discussion

This approval process has worked well since the Clinical Trial Policy was initiated. There are, however, additional Federal Agencies involved in clinical research that CMS thought appropriate to add to the list. The MedCAC agreed but recommended that additional language be added to require that the study be reviewed, approved, and funded. AHRQ recommended that the extension only be to agencies within DHHS, and continue with the VA and DOD. AHRQ did not believe that it would be appropriate for Medicare to cover the services and items in studies funded by any other Federal Agencies, because their missions differ substantially from that of the Medicare program and AHRQ was familiar with other Agencies' review processes. AHRQ also believed that any study funded by a Federal Agency would have been approved by that agency and thus the use of "approved" is redundant. AHRQ's major concern is that the protocol be reviewed and considered appropriate by the Federal Agency. We agree with the AHRQ changes and propose this modification for the new policy:

The following processes will assure that the general standards for a scientifically and technically sound clinical research study are met and assure that the research is conducted with AHRQ support pursuant to section 1142 of the Act:

Studies of health outcomes reviewed and funded by a program component of DHHS, the Veterans Administration, or the Department of Defense.

Trials supported by centers or cooperative groups that are funded by the NIH, CDC, AHRQ, HCFA, DOD and VA

Several Federal Agencies support nongovernmental centers or groups that routinely design and implement research studies. These centers and groups are deeming entities in the current policy. CMS suggested to the MedCAC that this option be continued with expansion to all Federal Agencies.

a) Public Comments

Commenters generally agreed with continuing this process.

b) MedCAC Recommendations

The MedCAC reviewed this current process for ensuring that covered trials meet the standards outlined in this policy. They made the following recommendation:

A study is deemed to have met the scientifically and technically sound general study standards if:

- The study has been reviewed and approved as scientifically sound by centers or cooperative groups that are funded by a Federal Agency.

c) AHRQ Recommendations

As discussed above, AHRQ's major concern in the approval process is that the study protocol is reviewed and considered appropriate by competent entities. In this instance, AHRQ was concerned that the level of review that these centers and groups provide for research studies is unknown and thus recommended additional language to emphasis the oversight needed by the Federal Agency to ensure that appropriate protocol review is performed. In sum, AHRQ expects that the Federal Agency will have reviewed the process that the supported center or group will use to approve and fund studies and have determined that process to be consistent with its own process.

The following processes will assure that the standards of scientifically and technically sound and safe research are met and assure that the research is conducted with AHRQ support pursuant to section 1142 of the Act:

Studies reviewed and approved by health care research centers or cooperative health care research groups, funded by one of the above Federal Agencies, provided that the Federal Agency reviews and approves the applicant research centers' or cooperative research groups' subcontract and sub-grant funding requirements, selection procedures and oversight methods, and determines that those processes provide the same level of protocol review as provided by the supporting Federal Agency.

d) Discussion

Significant research involving Medicare beneficiaries, particularly in the cancer field, is designed and run by centers and groups supported by Federal Agencies. This was recognized in drafting the original policy and this "deeming" option was added. However, in the discussions leading up to this policy change, it became apparent that the actual study review process performed by these centers and groups was unknown. Thus, AHRQ has recommended additional language to ensure that the supporting Federal Agency reviews and approves the center or groups study review and approval process. We agree with the AHRQ recommendation and propose this modification for the new policy.

The following processes will assure that the standards of scientifically and technically sound clinical research study are met and assure that the research is conducted with AHRQ support pursuant to section 1142 of the Act:

Studies reviewed and approved by health care research centers or cooperative health care research groups, funded by one of the above Federal Agencies, provided that the Federal Agency reviews and approves the applicant research centers' or cooperative research groups' subcontract and sub-grant funding requirements, selection procedures and oversight methods, and determines that those processes provide the same level of protocol review as provided by the supporting Federal Agency.

Trials conducted under an Investigational New Drug application (IND) reviewed by the FDA

The current clinical trial policy deemed "trials conducted under an investigational new drug application (IND) reviewed by the FDA" as meeting the seven desirable characteristics. 21 C.F.R. Part 312 defines IND as an investigational new drug application. It further states that, "For purposes of this part, ''IND'' is synonymous with 'Notice of Claimed Investigational Exemption for a New Drug". Part 312 defines *investigational new drug* as a new drug or biological drug that is used in a clinical investigation, including a biological product that is used in vitro for diagnostic purposes. The terms ''investigational drug'' and ''investigational new drug'' are deemed to be synonymous for purposes of Part 312. Before any human studies of an investigational new drug can begin, an IND must be submitted to the Agency containing, among other things, the protocol(s), information on pharmacological and toxicological studies of the drug in animals or in vitro, and information on previous human experience with the drug (21 C.F.R. 312.23(a)).

After a sponsor submits an IND to FDA, the IND goes into effect 30 days after FDA receives it, unless either FDA notifies the sponsor earlier than 30 days that the study may begin, or FDA places the study on clinical hold under 21 C.F.R. 312.42. FDA may also place an ongoing study on clinical hold if it finds that the grounds for clinical hold exist.

a) Public Comments

Commenters generally agreed with continuing this process.

b) MedCAC Recommendations

The MedCAC reviewed this current process for ensuring that covered trials meet the standards outlined in this policy. They made the following recommendation:

A study is deemed to have met the scientifically and technically sound general study standards if:

- The study is conducted under an IND application that has been reviewed and approved by the FDA.

c) AHRQ Recommendations

AHRQ agreed that it is important that studies conducted under an IND be reviewed by FDA for the quality of study design. This requirement for FDA review of studies conducted under an IND is present in the current policy. Because “approval” is not the operative term for the conclusion FDA reaches for IND studies under the Federal Food, Drug, and Cosmetic Act, this term, as recommended by the MedCAC, cannot be used. However, AHRQ does recommend that covered studies have protocols reviewed by FDA and not have had the IND application put on hold due to FDA concerns about safety or study design. AHRQ recommended the following language:

The following processes will assure that the standards of scientifically and technically sound and safe research are met and assure that the research is conducted with AHRQ support pursuant to section 1142 of the Act:

Studies conducted under an Investigational New Drug (IND) when the FDA has reviewed the protocol and the IND has not been put on hold.

d) Discussion

Studies conducted under an IND provide Medicare beneficiaries with options to voluntarily try previously unapproved drugs and new indications for approved drugs within the controlled environs of a clinical study. We wish to continue that. We agree with AHRQ’s recommendations that covered studies should include only those that have been reviewed by FDA and not put on hold due to safety or study design issues. This requirement is not new; it is present in the current policy. However, we want to emphasize that coverage of clinical services for Medicare beneficiaries participating in a study conducted under an IND is only effective after the FDA has reviewed the protocol and the application has not been put on hold. Therefore, we propose adding the following language to the new policy:

The following processes will assure that the standards of scientifically and technically sound clinical research are met and assure that the research is conducted with AHRQ support pursuant to section 1142 of the Act:

Studies conducted under an Investigational New Drug (IND) when the FDA has reviewed the protocol and the IND has not been put on hold.

Drug trials that are exempt from having an IND

The current Clinical Trial Policy states that drug trials that are exempt from having an IND under 21 CFR 312.2(b)(1) will be deemed automatically qualified until the qualifying criteria are developed and the certification process is in place.

At that time, the principal investigators of these trials would certify that the trials met the qualifying criteria in order to maintain Medicare coverage of routine costs. This certification process was intended only to affect the future status of the trial and not to be used to retroactively change the earlier deemed status. This option was to have been removed once the self-certification process was implemented.

As stated in 21 CFR, part 312, sponsors who wish to study a drug or biological product in humans generally must submit an IND to the FDA. However, these regulations also provide for the exemption of some studies from the requirement to submit an IND if they meet certain criteria. For example, the clinical investigation of a drug product lawfully marketed in the U.S. is exempt from the IND requirements if all of the following apply:

- The study is not intended to be reported to the FDA as a well-controlled study in support of a new indication or any other significant change in the product labeling.
- The drug is lawfully marketed as a prescription drug product and the study is not intended to support a significant change in the advertising for the product.
- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- The study is conducted in compliance with institutional review board (IRB) and informed consent regulations set forth in parts 56 and 50 (21 CFR parts 56 and 50).
- The study is conducted in compliance with section 312.7 (promotion and charging for investigational drugs).

CMS proposed deleting this category.

a) Public Comments

All of the comments CMS received on this topic advocated continued “deemed” status for IND Exempt trials, since they provide incentives for innovation. Commenters indicated that the FDA guidance has been supportive of IND Exempt trials, and had been regulating the process for conducting IND Exempt studies for some time through its requirements that IND Exempt trials receive monitoring from Institutional Review Boards (IRBs).

Some commenters questioned CMS’ statutory authority to expand Federal oversight of IND Exempt trials beyond FDA’s regulations. One commenter argued that any change CMS would propose regarding IND Exempt trials would need to be issued in the form of a regulation, issued jointly with the FDA.

b) MedCAC Recommendations

The MedCAC recommended deleting the deemed status of IND Exempt trials and developing another process for reviewing and approving these trials. As an alternative, they proposed that CMS develop a mechanism to certify other entities to deem research studies. Examples of deeming entities include professional societies, private foundations, academic health centers, and university scientific review panels. The committee urged that any process for deeming include representatives of the patient and provider community.

c) AHRQ Recommendations

AHRQ also agreed with deleting this process.

d) Discussion

CMS agrees that FDA retain full control of the IND and IND Exempt regulatory frameworks. Our intention in this policy is to stipulate the conditions under which Medicare will judge whether a trial is being conducted under scientifically and technically sound principles. IND Exempt trials do not have FDA oversight and thus have no external process for ensuring that the standards of this Medicare policy are being met. Thus, we propose that this approval process be removed and that studies that are IND Exempt meet the other criteria in this policy.

2. Self-certification

The other option outlined in the current policy for ensuring that the requirements of the policy were met was self-certification. CMS did not implement this process and recommended that this process be deleted in the new policy.

a) Public Comments

Commenters disagreed as to whether this was an advisable change to the policy. While several commenters supported this change, commenters representing the research and manufacturing sectors disagreed that CMS should delete the never-implemented self-certification process from the new policy. These commenters remarked that developing an alternate process for studies without Federal funding is integral to assuring broad access to clinical research participation for all Medicare beneficiaries. Since the self-certification provision did not materialize, these commenters encouraged CMS to convene a multi-stakeholder panel to develop criteria for covering the costs associated with “non-deemed” trials. They urged that a study’s qualifications should be based on scientifically sound criteria, not its funding source.

b) MedCAC Recommendations

MedCAC agreed with deleting this option.

c) AHRQ Recommendations

AHRQ agreed with deleting this option, but offered to engage with CMS and interested stakeholder groups in discussions for a process of self-certification or other alternative third party review processes that can be used to assure that the AHRQ and CMS standards are met for other studies that do not fall under the recommended research study approval processes.

d) Discussion

CMS believes that qualified trials need oversight beyond that provided by the trial investigators. CMS realizes that research protocols that are judged to be sound by a Federal Agency but are not funded may go on to be funded by another source. Despite the initial government approval of the study design, the study will no longer be subjected to Federal oversight. In addition, many studies have not been through a peer review process. In both cases, investigators may request certification to be eligible to receive Medicare payment for items or services provided in the trial. While we wish to encourage voluntary participation in high quality studies by Medicare beneficiaries, we do not believe self-certification is sufficient. We propose deletion of the self-certification in the new policy. We are committed to engaging the public in addressing this issue in the future.

3. Additional Options

***Post-approval studies*.**

CMS and FDA have collaborated recently in the design and implementation of several post approval studies for FDA regulated devices. FDA has authority for ordering post approval studies of drugs and devices, for which the agency generally reviews and approves the protocols. We recommended that in those instances in which FDA has required and approved a post-marketing study that those studies be added to the list of approved studies.

a) Public Comments

Commenters did not address this issue.

b) MedCAC Recommendations

The MedCAC reviewed the current process for ensuring that covered trials meet the standards outlined in this policy. They made the following recommendation:

A study is deemed to have met the scientifically and technically sound general study standards if:

- The study has been required and reviewed and approved by the FDA as a post-approval study.

c) AHRQ Recommendations

AHRQ agreed with the recommendations of the MedCAC for ensuring studies meet the standards outlined in the policy with the language revised as stated:

The following processes will assure that the standards of scientifically and technically sound and safe research are met and assure that the research is conducted with AHRQ support pursuant to section 1142 of the Act:

Studies that are required and approved by FDA as post-approval studies.

d) Discussion

Post-approval studies required by the FDA provide information for providers and patients about longer term outcomes that are seen with primary trials. While this is most common for devices, limited studies are also required for drugs. MedCAC agreed, as did AHRQ, that adding this approval process would add to the level of evidence for that particular technology. Thus, we are proposing the addition of the following approval process to the new policy:

The following processes will assure that the general standards for a scientifically and technically sound clinical research study are met and assure that the research is conducted with AHRQ support pursuant to section 1142 of the Act:

The study is required and approved by FDA as a post-approval study.

Coverage with Evidence Development

CMS proposed that an NCD may require specific studies using coverage with evidence development (CED) as described more fully in our July 12, 2006 guidance document (http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8).

a) Public Comments

Commenters responded to this issue by inquiring about the relationship between the proposed CRP and CMS' CED initiative. Most commenters agreed that tying CED with the CRP is a positive policy change—several commenters voiced support that linking these policies could increase access for Medicare beneficiaries. Commenters agreed that using the NCD process for this element of the policy would provide predictability and clarity for the public and researchers, while establishing an explicit process for requesting, evaluating, and implementing decisions to cover these items or services.

Some commenters voiced concerns about the potential overutilization of this approach. A Federal commenter suggested that CMS work with other Federal Agencies, such as NIH, to vet coverage of clinical trials so that CMS pays for studies that can achieve public health goals. This notion was extended by commenters in the private sector, who recommended that these processes be available to the public through a transparent collaboration process. Only one commenter provided negative feedback on this issue, criticizing this approach as detrimental to the evidence-based processes that CMS currently uses to make coverage decisions.

b) MedCAC Recommendations

The MedCAC agreed with this proposal and recommended the following language:

CMS will use the NCD process to define standards for specific qualified studies under CED. The NCD process will follow statute, allow public comments, and result in legally binding policy.

c) AHRQ Recommendations

AHRQ agreed with the recommendations of the MedCAC for ensuring studies meet the standards outlined in the policy with the suggested language:

The following process will assure that the standards of scientifically and technically sound and safe research are met and assure that the research is conducted with AHRQ support pursuant to section 1142 of the Act:

The study is required as an outcome of the National Coverage Determination process.

d) Discussion

We agree that utilization of CED should occur within the confines of the national coverage process. Not only does this provide transparency, reproducibility, and predictability to the coverage of investigational costs—it also precludes over-utilization and ensures that CMS' evaluation of these coverage issues will occur within an evidence-based framework. Both the MedCAC and AHRQ agreed with this recommendation and suggested revisions.

The AHRQ revision is clear and straightforward and we propose to that to the new policy:

The following processes will assure that the general standards for a scientifically and technically sound clinical research are met and assure that the research is conducted with AHRQ support pursuant to section 1142 of the Act:

The study is required as an outcome of the NCD process using CED.

Other Options

The public, MedCAC and AHRQ suggested a number of other options for approving trials.

a) Public Comments

Since the self-certification provision did not materialize, commenters encouraged CMS to convene a multi-stakeholder panel to develop criteria for covering the costs associated with "non-deemed" trials. They urged that a study's qualifications should be based on scientifically sound criteria, not its funding source.

b) MedCAC Recommendations

The MedCAC proposed that CMS should develop a mechanism to certify other entities to approve research studies. Examples of potential certifying entities include professional societies, private foundations, academic health centers, and university scientific review panels.

c) AHRQ Recommendations

AHRQ recognized the need for a process to assure that the standards of scientifically and technically sound and safe research are met for other types of studies, including IND-Exempt studies and studies on orphan drugs that do not fall under one of the above processes, and other clinical studies. They suggested that several issues remain for implementation of other potential processes such as self-certification or other methods, including how to:

- Reliably identify studies that are unsafe or of poor scientific quality;
- Assure the validity, reliability and rigor of the review process; and
- Assure that the studies have a process for monitoring and overseeing adverse events and unforeseen outcomes, such as a Data Safety Monitoring Board or other data and safety monitoring plan.

AHRQ offered to engage with CMS and interested stakeholder groups in discussions of these issues in order to make recommendations for a process of self-certification or other alternative third party review processes that can be used to assure that the AHRQ and CMS standards are met for other studies that do not fall under the processes described above.

d) Discussion

CMS agrees with the need to explore alternative processes for approving other types of studies such as IND Exempt studies and studies of orphan drugs. In addition, most studies of medical and surgical procedures have no Federal Agency review and, as such, were not covered under the original policy. CMS and AHRQ will engage the public in a discussion of various supportable options.

4. Medicare-specific and NCD CED Standards

The current clinical trial policy does not address how the studies were to be assessed as to whether or not the Medicare-specific standards are met. In addition, our proposed policy included the ability to require additional Medicare-specific standards for clinical research studies that have been identified through the NCD process using CED. We propose to clarify in the CRP that as with all other items and services provided to Medicare beneficiaries, CMS will use routine processes to ensure that the Medicare-specific standards and any standards required through the NCD process using CED are met.

CMS will add the following language to the new policy outlining the approval process of the Medicare-specific standards:

As with all other items and services provided to Medicare beneficiaries, Medicare contractors will use routine processes to ensure that the Medicare-specific standards and NCD CED standards are met.

Approval Process Summary

CMS will add the following language to the new policy outlining the approval process for research studies:

As with all other items and services provided to Medicare beneficiaries, Medicare contractors will use routine processes to ensure that the Medicare-specific standards and NCD CED standards are met.

The following processes will assure that the general standards of scientifically and technically sound clinical research study are met and assure that the research is conducted with AHRQ support pursuant to section 1142 of the Act. Therefore, clinical research studies will be "deemed" to have met the standards in the policy.

1. *Studies of health outcomes reviewed and funded by a program component of DHHS, the Veterans Administration or the Department of Defense.*
2. *Studies reviewed and approved by health care research centers or cooperative health care research groups, funded by one of the above Federal Agencies, provided that the Federal Agency reviews and approves the applicant research centers' or cooperative research groups' subcontract and sub-grant funding requirements, selection procedures and oversight methods, and determines that those processes provide the same level of protocol review as provide by the supporting Federal Agency.*
3. *Studies conducted under an Investigational New Drug (IND) when the FDA has reviewed the study protocol and the IND application has not been put on hold.*
4. *The study is required and approved by FDA as a post-approval study.*
5. *The study is required as an outcome of the NCD process using CED.*

D. COVERED SERVICES

CMS proposed several changes to the definitions of covered items and services to the MedCAC. AHRQ in general did not discuss nor provide recommendations to this section in that its interests are to ensure that the research study is conducted pursuant to section 1142 of the Act and not in the particular items or services covered.

1. Routine Clinical Services

The 2000 Clinical Trial Policy NCD covers “routine costs” for beneficiaries participating in covered clinical trials. The definition of “routine costs” has resulted in inconsistent coverage of beneficiaries in clinical studies among providers and Medicare contractors that process and pay claims. Typically, the Agency will define the items or services that are covered, and then assign a payment amount. Therefore, we are suggesting that we no longer discuss the “costs” that are covered in clinical studies but rather to define those items and services that are covered. We propose that we now title these items and services “routine clinical services.”

In addition, we recommended modifying the definition for clarity:

- Items and services that are available to Medicare beneficiaries outside of a clinical study, other than items or services that meet the definition of investigational clinical services;
- Only those items and services used for patient management within the study;
- Items or services required solely for the provision of the investigational item or service (e.g., administration of a non-covered chemotherapeutic agent);
- The clinically appropriate monitoring of the effects of the item or service (e.g., blood tests to measure tumor markers); and
- Items or services required for the prevention, diagnosis, or treatment of complications (e.g., blood levels of various parameters to measure kidney function).

a) Public Comments

While several commenters indicated that our discussion of routine costs in the 2000 Clinical Trial Policy continued to be sufficient and appropriate, several more asked us to clarify it or provided suggested revisions. These commenters mentioned that CMS should either retain the current scope of benefits or expand them—no one indicated that CMS should withdraw existing coverage.

Commenters asked for several points of clarification on the definition of routine costs, including clarification of the terms “conventional care” and “routine care.” Commenters noted that the current definition of routine costs does not provide predictability regarding which costs Medicare will cover, and which costs Medicare will disallow as “research costs” or “investigational costs.” In addressing these concerns, commenters provided alternative language for CMS to consider in revising the definition of routine costs. These definitions varied, but most included provisions for evaluation of routine costs on a patient-by-patient basis, and provided for coverage of items or services that the physician determined were medically necessary to manage the patient while participating in the trial.

Some commenters expressed support for extending the coverage of routine costs beyond the current scope. Commenters suggested numerous opportunities for Medicare to cover these costs—including several suggestions that all qualified studies should be eligible for coverage of routine costs, regardless of funding source. A few commenters suggested that Medicare should cover costs associated with prevention studies (including studies of asymptomatic patients). Not all commenters agreed with this approach—several commenters indicated that the scope of routine costs under the 2000 Clinical Trial Policy continues to be appropriate.

Some commenters remarked that physicians are in the best position to determine routine costs of care at point-of-service, as they determine reasonable and necessary services for patients outside of trials. Other commenters disagreed, stating that sponsors and investigators should work together with Medicare and compliance professionals *before* a trial begins to delineate routine costs provided under the trial.

Many commenters suggested that the standard of “conventional care” is problematic in multi-center trials, since different Medicare contractors may interpret claims differently, depending upon geographic variations in care patterns. As such, some commenters remarked that CMS should delineate routine costs only at the national level.

b) MedCAC Recommendations

The MedCAC agreed with the proposed definition of routine clinical services.

c) Discussion

Our current definition of routine costs has been confusing. The intent was to provide coverage for those items and services that are provided outside the trial but to exclude the item or service under investigation even if covered outside the trial. Some of the language in the current policy was confusing because it stated that conventional care was covered. Some interpreted “conventional care is covered” to mean that it was covered even when it was the investigational item or service. Thus, we recommend that we define routine clinical services as those items and services that are available to Medicare beneficiaries outside the study, but are not explicitly the item or service being evaluated for its effect on health outcomes (i.e., not the investigational item or service), only when those items and services are used for patient management within the study. It includes items or services required solely for the provision of the investigational item or service (e.g., administration of a non-covered chemotherapeutic agent), the clinically appropriate monitoring of the effects of the item or service (e.g., blood tests to measure tumor markers), or the diagnosis, prevention (e.g., blood levels of various parameters to measure kidney function), or treatment of complications. It does not include any items or services that meet the definition of investigational clinical services. Items and services provided solely for purposes of obtaining data for study analyses that are not intended or indicated for patient management will not be included in this definition (e.g., serial testing of a serum marker to assess the impact of the investigational item on the marker, when no clinical event justifies the assessment of that marker).

We agree that the current definition of routine costs is not clear and therefore propose a revised definition that continues the intent of the 2000 executive memorandum. MedCAC agreed with these recommended changes and we propose to make these modifications in the new policy. Routine clinical services will continue to include those Medicare services that are provided to patients outside the study, are not the investigational item or service, are not provided free to Medicare beneficiaries, are not provide free to all other enrollees and are used to manage the patient’s care and not for study purposes only.

We are proposing that the definition of routine clinical services include:

- *Items and services that are available to Medicare beneficiaries outside of a clinical study, other than items or services that meet the definition of investigational clinical services;*
- *Only those items and services used for patient management within the study;*
- *Items or services required solely for the provision of the investigational item or service (e.g., administration of a non-covered chemotherapeutic agent);*
- *The clinically appropriate monitoring of the effects of the item or service (e.g., blood tests to measure tumor markers); and*
- *Items or services required for the prevention, diagnosis, or treatment of complications (e.g., blood levels of various parameters to measure kidney function).*

2. Administrative Services

The current clinical trial policy does not define administrative services of carrying out trials. CMS proposed the following definition:

Administrative services are defined as all nonclinical services, such as investigator salaries; protocol development; recruiting participants; data quality assurance activities, statistical analyses; dissemination of findings; and study management.

CMS also recommended noncoverage of these services.

a) **Public Comments**

CMS did not receive public comments about this issue.

b) MedCAC Recommendations

The MedCAC agreed with the proposed definition of administrative services and with the noncoverage of these within approved clinical trials

c) Discussion

While the current Clinical Trial NCD does not explicitly address costs of administering trials within clinical studies, Medicare's long standing practice has been to non-cover these. We proposed to the MedCAC that the policy explicitly define these administrative services as all nonclinical costs such as investigator salaries; protocol development; recruiting participants; data quality assurance activities, statistical analyses; dissemination of findings; and study management. We also proposed to the MedCAC that these be noncovered. The MedCAC agreed. We also want to ensure that previously noncovered administrative services are clearly continued in this definition. The current policy specifically excludes services not involved in direct clinical management and we will add that wording also. Thus, we propose adding the following definition to the new policy:

Administrative services are defined as *all nonclinical services, such as investigator salaries; protocol development; recruiting participants; data quality assurance activities, statistical analyses; dissemination of findings; and study management. Administrative services also include clinical services provided to solely satisfy data collection and analysis needs that are not used in the direct clinical management of the patient.*

The activities associated with this definition will be explicitly non-covered.

3. Investigational Clinical Services

The current policy does not define investigational costs or services. It does exclude the costs of the investigational item or service from the definition of routine costs, even if covered outside the study. We recommended a definition of:

Investigational clinical services are those items and services that are being investigated as an objective within the study.

CMS also recommended three circumstances under which investigational clinical services would be covered:

The item or service in a clinical trial is an item or service that is currently available to the Medicare beneficiary and thus eligible for coverage outside the study;

The item or service is required through the CED process in an NCD; or

The item has been designated by the FDA as an HUD, has received HDE status and is the investigational item or service in a study that meets the requirements of the policy.

a) Public Comments

CMS did not request public comment on a specific definition of investigational clinical services. However, commenters generally were in favor of adding coverage for the investigational item if it is covered outside the trial.

Most commenters also agreed that tying CED with the CRP is a positive policy change—several commenters voiced support that linking these policies could increase access for Medicare beneficiaries. Commenters agreed that using the NCD process for this element of the policy would provide predictability and clarity for the public and researchers, while establishing an explicit process for requesting, evaluating, and implementing decisions to cover these items or services.

Some commenters voiced concerns about the potential overutilization of this approach. A Federal commenter suggested that CMS work with other Federal Agencies, such as NIH, to vet coverage of clinical trials so that CMS pays for studies that can achieve public health goals. This notion was extended by commenters in the private industry, who recommended that these processes be available to the public through a transparent collaboration process. Only one commenter provided negative feedback about this issue, criticizing this approach as detrimental to the evidence-based processes that CMS currently uses to make coverage decisions.

All comments received about HUDs advocated coverage of costs in the context of trials for HUDs that have been granted humanitarian device exemptions (HDEs) from the FDA. Commenters remarked that denying HUD costs is a barrier to bringing products to market because of the burdens placed upon sponsors, hospitals, and physicians to shoulder the costs. One commenter suggested that HUD costs in addition to the routine care should be covered; however, this should be restricted to the use of HUDs in randomized controlled trials. Some commenters indicated that CMS had already been providing coverage of HUDs under local coverage policies.

b) MedCAC Recommendations

MedCAC agreed with this definition. The panel discussed HUDs in detail. In general, the panel agreed that the goal of developing evidence of the effectiveness of HUD's was worthy. However, several members noted that because the HUD designation means that a device is intended for a population of fewer than 4,000 patients yearly, the available pool of candidates for a well-designed study may often be inadequate. Members also expressed concern that implementing coverage of HUDs may encourage over reliance on the HDE designation. After discussion, the committee recommended that HUDs with an HDE be covered when they are the investigational item in covered research studies both when the item is noncovered nationally and in all other circumstances.

c) AHRQ Recommendation

AHRQ did not specifically address coverage of HUDs with an HDE. However, AHRQ did recognize the need for a process to assure that the standards of scientifically and technically sound and safe research are met for other types of studies, and included studies of humanitarian use devices that do not fall under one of the above processes

d) Discussion

Definition

There was general agreement about the definition of investigational clinical services and we propose to add this definition to the new policy:

Investigational clinical services are those items and services that are being investigated as an objective within the study.

The item or service is currently available to the Medicare beneficiary and thus eligible for coverage outside the study.

In some instances, the investigational item or service in a clinical trial is an item or service that is currently available to the Medicare beneficiary and thus eligible for coverage outside the trial. We recommended coverage of these items and services in the study. While it is not completely clear as to the reasoning that was used in the current policy for not covering items and services that would be covered outside the trial, we believe it developed out of a longstanding CMS position of not paying for experimental or investigational items or services. However, the item or service that is being investigated as an objective within a study is not necessarily experimental or investigational. If it has been determined to be reasonable and necessary under 1862(a)(1)(A), then it has been determined to not be experimental or investigational. Thus, we believe it appropriate to cover these items and services within a covered research study even if they are the item under investigation.

The MedCAC concurred with the CMS recommendation and we propose adding this condition for coverage of the investigational item or service to the new policy.

The item or service in a clinical research study is an item or service that is currently available to the Medicare beneficiary outside the study (i.e., the item or service is covered under § 1861(a)(1)(A) of the Act).

Coverage with evidence development (CED)

As discussed above, in July 2006, the Agency posted guidelines entitled, “National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development.” In addition to using this process to define additional standards that specific research studies must meet, we proposed to cover the investigational services required by CED. In this circumstance, this could include items and services that are not routinely covered outside the trial. The MedCAC agreed with this concept and we are proposing to add this to the new policy.

The item or service is required as a condition of coverage through the National Coverage Determination (NCD) process using Coverage with Evidence Development (CED).

Humanitarian Use Devices

CMS currently has no national policies for the coverage of HUDs with an HDE. Contractors may choose to cover these though they have done so in very limited circumstances. CMS asked the MedCAC to consider circumstances under which CMS should cover HUDs with an HDE both when non-covered at a national level and when there is no national coverage determination. CMS specifically asked that the MedCAC consider broadly covering HUDs with an HDE when they are the investigational item in a covered research study.

While CMS understands and agrees with the Committee’s support for clinical studies involving HUDs, we are proposing that the revised policy not include a separate provision for HUDs. This would allow for coverage of HUDs under the same standards as outlined in this policy for other items or services under study. We believe that the most appropriate coverage of HUDs would be through the CED process in an NCD.

E. ADDITIONAL ISSUES

1. Medicare Secondary Payer Rules

Public Comments

CMS received comments from all sectors of the healthcare community about this topic. The nature of these comments varied; however, many of them focused on the effect of Medicare Secondary Payer provisions when trial protocols state that sponsors will pay for beneficiaries' costs of care in the event of complications. Commenters pointed to this issue as an administrative barrier to Medicare beneficiaries' participation in clinical studies. Commenters encouraged CMS to address, in a public policy document, the provisions of Medicare Secondary Payer rules in the context of the CRP. While these concerns extend beyond the scope of an NCD, we have shared them with our colleagues in the Medicare Secondary Payer program area who will provide guidance outside this policy.

2. Medicare Advantage Plans

Public Comments

Numerous commenters expressed concern about the logistical framework by which beneficiaries in Medicare Advantage (MA) plans participate in covered trials. In particular, commenters urged CMS to reduce the cost-sharing that currently applies when enrollees in MA plans receive covered clinical trial services. The commenters state that MA plans currently charge MA enrollees coinsurance amounts commensurate to those charged to beneficiaries who participate in the original Medicare plan. We have referred these concerns to the CMS organization that administers the Medicare Advantage program, and note that they do not involve a coverage issue that falls within the scope of a national coverage determination, but rather the cost-sharing amounts that apply to a covered service.

Discussion

MA Plans are offered by private health plans ("MA Organizations") that contract with CMS to provide Medicare covered services to Medicare beneficiaries who choose to enroll in the MA plan. The cost-sharing amounts that apply to particular services covered under an MA contract are determined by the MA organization offering the plan, subject to CMS approval. We will attempt to clarify the MA payment issues that have raised concern.

Generally, Medicare beneficiaries enrolled in MA plans get all Medicare-covered health care through that plan, and MA organizations are paid an amount established by statute to cover such services. When Medicare expands coverage under an NCD, and this expansion of coverage meets specified cost thresholds, MA organizations services are not required to cover such expanded services under their contracts until adjustments can be made to the payments made to MA organizations to reflect the costs of the new covered services. As a result, when the current Clinical Trial Policy was first implemented in 2000, the services newly covered under this policy were covered for MA plan enrollees directly by Medicare, as if the enrollees were not enrolled in an MA plan. In subsequent years, CMS decided that the best way to pay MA organizations for Clinical Trial services they were now required to cover would be to pay for these services on a fee-for-service basis. As a result, MA organizations have chosen to provide that the cost-sharing that applies to Clinical Trial services covered under an MA plan would be the same that applies under original Medicare. More information about the MA program can be found at: http://www.cms.hhs.gov/manuals/downloads/mc86c01.pdf.

3. Exclusions

A number of data collection processes, while potentially meeting the definition of a clinical research study in this policy, are based upon previously collected data or data collected in such a manner as to not influence patient management or health outcomes. The clinical services that are provided as the basis for these data collection processes may be determined to be reasonable and necessary under section 1862(a)(1)(A). These include:

- Simple non-comparative case reports and case series;
- Retrospective studies that evaluate events that have already occurred including studies that rely exclusively on previously collected administrative records, medical data or other available data;
- Quality assessment, quality improvement, or performance improvement studies; and
- Prospective studies in which natural human behavior is observed in a way that does not intentionally or unintentionally change or potentially change the behavior of patients, physicians and other clinical staff, control subjects, healthy volunteers, or caretakers; in which there is no assigned or pre-specified intervention that intentionally or unintentionally changes or potentially changes the behavior of patients, physicians and other clinical staff, control subjects, healthy volunteers, or caretakers; and in which there is no assigned or pre-specified intervention that changes or potentially changes medical care, medical decision-making or any medical treatments.

As stated in the Background section, the goal of this policy is to increase access to Medicare beneficiaries to quality clinical research studies. The concerns raised revolve around changes in patient management that, while having the potential to improve health outcomes, also may result in no improvements or in worse outcomes. Good study design and well-informed patients lessen the risk potential. The studies listed above are either studying care that has already been provided or will observe care as it is provided without intervening. These types of studies provide valuable information to patients and providers but do not require the same safeguards outlined in this policy. Therefore, we will not require these studies to meet the standards or approval processes outlined in this policy. All human subject protections and patient privacy rules will continue to apply.

V. Conclusion

We believe that the changes CMS is proposing to the current Clinical Trial Policy are consistent with the original Executive Memorandum and with the goals we stated at the beginning of this process:

- Allow Medicare beneficiaries to participate in research studies;
- Encourage the conduct of research studies that add to the knowledge base about the efficient, appropriate, effective, and cost-effective use of products and technologies in the Medicare population, thus improving the quality of care that Medicare beneficiaries receive; and,
- Allow Medicare beneficiaries to receive care that may have a health benefit, but for which evidence for the effectiveness of the treatment or service is insufficient to allow for full, unrestricted coverage.

We are especially encouraged by the support and recommendations to strengthen the approval processes to ensure that our beneficiaries, when participating in research studies, have greater assurance that the study will be of good quality and of benefit not only to them but to all Medicare beneficiaries.

The following is a summary of the proposed changes to the current policy:

The Centers for Medicare & Medicaid Services (CMS) is proposing the following revisions to the Medicare National Clinical Trial Policy:

1) Rename the policy, the Clinical Research Policy (CRP).

2) Add a definition of research.

3) Continue the seven highly desirable characteristics and rename them “general standards for a scientifically and technically sound clinical research study” and add an additional standard: “The research study must have a written protocol.”

4) Revise the requirements that qualify a clinical study for Medicare coverage by renaming them “Medicare-specific standards,” eliminating the first, and combining and modifying the second and third requirements for greater clarity. Add the following Medicare-specific requirements:

- The research study must be registered on the ClinicalTrials.gov website prior to the enrollment of the first study subject.
- The research study protocol must specify and fulfill method and timing of public release of results.
- The research study must have explicitly discussed inclusion criteria and considered relevant subpopulations (as defined by age, gender, race/ethnicity, socioeconomic, or other factors) in the study protocol.
- The protocol must contain a discussion of how the results will generalize to the Medicare population.

5) The NCD process may establish additional standards through Coverage with Evidence Development (CED).

6) Rename routine costs to “routine clinical services” and clarify the definition.

7) Add a definition of administrative services required to carry out studies and clarify that Medicare will not cover administrative services.

8) Add a definition for investigational clinical services and cover those services when the service is available to Medicare beneficiaries that are not participating in a study or when it is required through CED.

9) Clarify those processes that ensure that both the Medicare-specific standards and the general standards for a scientifically and technically sound clinical research study are met.

- General standards:

    1. Studies approved by DHHS Agencies, the Veterans Administration or the Department of Defense.
    2. Studies approved by research centers or cooperative groups funded by one of the above Federal Agencies who have approved their process.
    3. Studies conducted under an Investigational New Drug (IND) where the protocol has been reviewed by the FDA.
    4. Studies that FDA requires and approves as a post-approval commitment.
    5. Studies required through CED.
- Medicare specific standards: CMS will use routine processes to ensure that the Medicare-specific standards are met.

10) Remove the following options for “deeming” studies:

- Self-certification process.
- IND Exempt studies.

We are requesting public comments about this proposed determination pursuant to Section 731 of the Medicare Modernization Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

Appendices:

A – Proposed NCD Language

B – Current Clinical Trial Policy NCD

APPENDIX A

NCD Manual 310.1: Clinical Research Policy

Medicare payments under the Clinical Research Policy are based on §1862(a)(1)(E) and §1142 of the Social Security Act.

Effective for items and services furnished on or after XXX XX, 2007, Medicare covers routine and/or investigational clinical services, under the circumstances described more fully below, in approved research studies. The subject or purpose of the study must be the evaluation of an item or service that falls within a Medicare benefit category under Part A or Part B (e.g., physicians' service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids). In addition, Medicare covers reasonable and necessary items and services used to prevent, diagnose, and treat complications arising from participation in these research studies. 42 C.F.R. § 405.207(b)(1).

All other Medicare program rules apply.

1. Definitions

Administrative services: Administrative services are defined as all non-clinical services, such as investigator salaries; protocol development; recruiting participants; data quality assurance activities; statistical analyses; dissemination of findings; and study management. Administrative services also include clinical services provided to solely satisfy data collection and analysis needs that are not used in the direct clinical management of the patient.

Clinical research: Clinical research is the observation of events in groups of individuals who share a particular characteristic, such as a symptom or illness; or who have the same treatment or diagnostic test provided for a symptom or illness. Inferences are made based on comparisons of predefined health outcomes among groups. Procedures are in place to assure that the rights, safety, and wellbeing of research study participants are protected. Research studies must conform to all applicable Federal regulations concerning human subject protection and privacy including 45 C.F.R. Part 46 and Parts 160 and 164.

Some examples of the types of clinical studies that might be supported follow, but this list should not be considered an all-inclusive list:

- Randomized controlled trials and other comparative clinical studies of effectiveness and comparative effectiveness;
- Observational clinical studies of outcomes of specific interventions, primary and secondary prevention strategies, or of implemented strategies related to delivery of care or testing of hypotheses regarding health services research; and
- Clinical studies of diagnostic tests, including measurements of sensitivity and specificity, and impact on physician decision making and patient outcomes.

General standards for a scientifically and technically sound clinical research study: A clinical research study that meets the general standards are listed below:

- The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- The research study does not unjustifiably duplicate existing studies.
- The research study design is appropriate to answer the research question being asked in the study.
- The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 C.F.R. Part 46. If a study is FDA-regulated, it also must be in compliance with 21 C.F.R. Parts 50 and 56.
- All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
- All research studies have a written protocol.

Investigational clinical services: Investigational clinical services are defined as those items and services that are being investigated as an objective within the study.

Medicare-specific standards for clinical research studies: An approved research study must meet the following standards:

- The clinical research study is not designed to exclusively test toxicity or disease pathophysiology. Research studies, including some Phase I trials, whose protocols commit to measuring therapeutic outcomes as one of the objectives, may meet this standard only if the disease being studied is chronic, life threatening, or debilitating.
- The research study is registered on the ClinicalTrials.gov website prior to the enrollment of the first study subject.
- The research study protocol specifies and fulfills method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early.
- The research study protocol must have explicitly discussed inclusion criteria and considered relevant subpopulations (as defined by age, gender, race/ethnicity, socioeconomic or other factors).
- The research study protocol contains a discussion of how the results will generalize to the Medicare population to infer whether Medicare patients may benefit from the intervention. In particular, the protocol describes the potential impact of age-specific and other factors on outcomes and whether the research study is powered sufficiently to draw conclusions with respect to the Medicare population.

National coverage determination Coverage with Evidence Development standards*:* CMS may require additional Medicare-specific standards for clinical research studies that have been identified through the NCD process using CED.

Routine clinical services: Routine clinical services include:

- items and services that are available to Medicare beneficiaries outside of a clinical study, other than items or services that meet the definition of investigational clinical services;
- only those items and services used for patient management within the study;
- items or services required solely for the provision of the investigational item or service (e.g., administration of a non-covered chemotherapeutic agent);
- the clinically appropriate monitoring of the effects of the item or service (e.g., blood tests to measure tumor markers); and
- items or services required for the prevention, diagnosis, or treatment of complications (e.g., blood levels of various parameters to measure kidney function).

2. Coverage of Clinical Services.

Routine Clinical Services. Using processes outlined in Section 4, Medicare covers routine clinical services in clinical research studies if those studies meet the general standards for a scientifically and technically sound clinical research study, the Medicare-specific standards, and if applicable, any NCD standards as defined in Section 1. Medicare does not cover routine clinical services when they are provided free to the Medicare beneficiary or when the study sponsor agreement with investigator sites or the informed consent documents provided to the patient specify that the clinical service will be provided free to all enrollees (§1862(a)(2); 42 CFR 411.4). All other Medicare program rules and policies apply for coverage of an item or service that meets the definition of routine clinical services.

Investigational Clinical Services. Using processes outlined in Section 4, Medicare covers investigational clinical services in clinical research studies if those studies meet the general standards for a scientifically and technically sound clinical research study, the Medicare-specific standards, and if applicable, any NCD standards, as defined in Section 1, and the investigational clinical service is:

- currently available to the Medicare beneficiary outside the study (i.e., the item or service is covered under § 1861(a)(1)(A) of the Act); or
- required as a condition of coverage through the National Coverage Determination (NCD) process using Coverage with Evidence Development (CED).

Medicare does not cover investigational clinical services when they are provided free to the Medicare beneficiary or when the study sponsor agreement with investigator sites or the study informed consent documents provided to the patient specify that the clinical service will be provided free to all enrollees (§ 1862(a)(2); 42 CFR 411.4).

3. Non-Coverage of Administrative Services.

Administrative services, as defined in Section 1, in a research study are not covered by Medicare.

4. Approval Process.

As with all other items and services provided to Medicare beneficiaries, Medicare contractors will use their standard processes to ensure that the Medicare-specific standards are met.

The following processes will assure that the general standards of scientifically and technically sound clinical research study are met and assure that the research is conducted with AHRQ support pursuant to section 1142 of the Act. Therefore, clinical research studies will be "deemed" to have met the standards in the policy.

- Studies of health outcomes reviewed and funded by a program component of DHHS, the Veterans Administration, or the Department of Defense.
- Studies reviewed and approved by health care research centers or cooperative health care research groups, funded by one of the above Federal Agencies, provided that the Federal Agency reviews and approves the applicant research centers' or cooperative research groups' subcontract and sub-grant funding requirements, selection procedures and oversight methods, and determines that those processes provide the same level of protocol review as provide by the supporting Federal Agency.
- Studies conducted under an Investigational New Drug (IND) when the FDA has reviewed the study protocol and the IND has not been put on hold.
- The study is required and approved by FDA as a post-approval study.
- The study is required as an outcome of the NCD process using CED.

5. Exclusions

A number of data collection processes, while meeting the broad definition of a clinical research study, are based upon previously collected data, or data collected in such a manner as to not influence current patient management or health outcomes. The clinical services that are provided as the basis for these data collection processes may be determined to be reasonable and necessary under §1862(a)(1)(A).

These include:

- Simple non-comparative case reports and case series;
- Retrospective studies that evaluate events that have already occurred including studies that rely exclusively on previously collected administrative records, medical data or other available data;
- Quality assessment, quality improvement, or performance improvement studies; and
- Prospective studies in which natural human behavior is observed in a way that does not intentionally or unintentionally change or potentially change the behavior of patients, physicians and other clinical staff, control subjects, healthy volunteers, or caretakers; in which there is no assigned or pre-specified intervention that intentionally or unintentionally changes or potentially changes the behavior of patients, physicians and other clinical staff, control subjects, healthy volunteers, or caretakers; and in which there is no assigned or pre-specified intervention that changes or potentially changes medical care, medical decision-making or any medical treatments.

These studies are not required to meet the standards or approval processes outlined in this policy. All human subject protections and patient privacy rules continue to apply.

6. Exceptions.

Medicare will pay for covered services in qualified research studies as defined in this policy unless CMS's Chief Medical Officer subsequently finds that the study does not meet the criteria outlined in this policy or the study jeopardizes the safety or welfare of Medicare beneficiaries.

Should CMS find that a study no longer qualifies for coverage, Medicare payment would be denied under §1862(a)(1)(E) of the Act. In the case of such a denial, the Medicare beneficiaries enrolled in the study would not be held liable (i.e., would be held harmless from collection) for the costs consistent with the provisions of §1879, 1842(l), or 1834(j)(4) of the Act, as applicable. Where appropriate, the billing providers would be held liable for the costs and fraud investigations of the billing providers and the study's principal investigator may be pursued.

7. Local Coverage Determinations

This policy does not withdraw Medicare coverage for items and services that may be covered according to local coverage determinations (LCD). For information about LCDs, refer to http://www.cms.hhs.gov/DeterminationProcess/04_LCDs.asp#TopOfPage, a searchable database of Medicare contractors' local policies.

8. Investigational Device Exemption (IDE)

This policy is not applicable to, and does not propose to change Medicare coverage according to the regulations on category A and categoryB investigational device exemptions (IDE) found in 42 CFR 405.201-405.215, 411.15, and 411.406.

9. Medicare Advantage Organizations

This policy does not propose to change Medicare regulations that require Medicare Advantage (MA) organizations to follow CMS' national coverage decisions. This NCD raises special issues that may require some modification of MA organizations' rules governing provision of items and services in and out of network. The items and services covered under this NCD are inextricably linked to the clinical studies with which they are associated and cannot be covered outside of the context of those clinical studies. MA organizations therefore must cover these services regardless of whether they are available through in-network providers. MA organizations may have reporting requirements when enrollees participate in clinical studies in order to track and coordinate their members' care, but cannot require prior authorization or approval.

10. Medicare Prescription Drug Benefit

This policy is not applicable to and does not propose any changes to Medicare policies for coverage of prescription drugs under Medicare Part D.

Appendix B

NCD for Routine Costs in Clinical Trials (310.1)

Publication Number

100-3

Manual Section Number

310.1

Version Number

1

Effective Date of this Version

9/19/2000

Implementation Date

9/19/2000

Benefit Category

Ambulance Services
Ambulatory Surgical Center Facility Services
Antigens
Artificial Legs, Arms, and Eyes
Audiology Services
Blood Clotting Factors for Hemophilia Patients
Bone Mass Measurement
Certified Nurse-Midwife Services
Certified Registered Nurse Anesthetist Services
Chiropractor Services
Clinical Nurse Specialist Services
Clinical Social Worker Services
Colorectal Cancer Screening Tests
Comprehensive Outpatient Rehabilitation Facility (CORF) Services

Critical Access Hospital Services
Dentist Services
Diabetes Outpatient Self-Management Training
Diagnostic Laboratory Tests
Diagnostic Services in Outpatient Hospital
Diagnostic Tests (other)
Diagnostic X-Ray Tests
Drugs and Biologicals
Durable Medical Equipment
Erythropoietin for Dialysis Patients
Extended Care Services
Eyeglasses After Cataract Surgery
Federally Qualified Health Center Services
Hepatitis B Vaccine and Administration
Home Dialysis Supplies and Equipment
Home Health Services
Hospice Care
Immunosuppressive Drugs
Incident to a physician's professional Service
Influenza Vaccine and Administration
Inpatient Hospital Services
Inpatient Psychiatric Hospital Services
Institutional Dialysis Services and Supplies
Leg, Arm, Back, and Neck Braces (orthotics)
Medical Nutrition Therapy Services
Nurse Practitioner Services
Optometrist Services
Oral Anticancer Drugs
Oral Antiemetic Drugs
Orthotics and Prosthetics
Osteoporosis Drug
Outpatient Hospital Services Incident to a Physician's Service
Outpatient Occupational Therapy Services
Outpatient Physical Therapy Services
Outpatient Speech Language Pathology Services
Partial Hospitalization Services
Physician Assistant Services
Physicians' Services
Pneumococcal Vaccine and Administration
Podiatrist Services
Post-Hospital Extended Care Services
Post-Institutional Home Health Services
Prostate Cancer Screening Tests
Prosthetic Devices
Qualified Psychologist Services
Religious NonMedical Health Care Institution
Rural Health Clinic Services
Screening for Glaucoma
Screening Mammography
Screening Pap Smear
Screening Pelvic Exam
Self-Care Home Dialysis Support Services
Shoes for Patients with Diabetes
Skilled Nursing Facility
Splints, Casts, Other Devices Used for Reduction of Fractures and Dislocations
Surgical Dressings
Transplantation Services for ESRD-Entitled Beneficiaries
X-ray, Radium, and Radioactive Isotope Therapy

Note: This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

Coverage Topic

Clinical Trials (Inpatient)
Clinical Trials (Outpatient)

Indications and Limitations of Coverage

Effective for items and services furnished on or after September 19, 2000, Medicare covers the routine costs of qualifying clinical trials, as such costs are defined below, as well as reasonable and necessary items and services used to diagnose and treat complications arising from participation in all clinical trials. All other Medicare rules apply.

Routine costs of a clinical trial include all items and services that are otherwise generally available to Medicare beneficiaries (i.e., there exists a benefit category, it is not statutorily excluded, and there is not a national noncoverage decision) that are provided in either the experimental or the control arms of a clinical trial except:

- The investigational item or service, itself;
- Items and services provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the patient (e.g., monthly CT scans for a condition usually requiring only a single scan); and
- Items and services customarily provided by the research sponsors free of charge for any enrollee in the trial.

Routine costs in clinical trials include:

- Items or services that are typically provided absent a clinical trial (e.g., conventional care);
- Items or services required solely for the provision of the investigational item or service (e.g., administration of a noncovered chemotherapeutic agent), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications; and
- Items or services needed for reasonable and necessary care arising from the provision of an investigational item or servicein particular, for the diagnosis or treatment of complications.

This policy does not withdraw Medicare coverage for items and services that may be covered according to local medical review policies or the regulations on categoryB investigational device exemptions (IDE) found in 42 CFR 405.201-405.215, 411.15, and 411.406. For information about LMRPs, refer to www.lmrp.net, a searchable database of Medicare contractors' local policies.

For noncovered items and services, including items and services for which Medicare payment is statutorily prohibited, Medicare only covers the treatment of complications arising from the delivery of the noncovered item or service and unrelated reasonable and necessary care. (Refer to MCM §§2300.1 and MIM 3101.) However, if the item or service is not covered by virtue of a national noncoverage policy in the Coverage Issues Manual and is the focus of a qualifying clinical trial, the routine costs of the clinical trial (as defined above) will be covered by Medicare but the noncovered item or service, itself, will not.

A. Requirements for Medicare Coverage of Routine Costs.Any clinical trial receiving Medicare coverage of routine costs must meet the following three requirements:
   1. The subject or purpose of the trial must be the evaluation of an item or service that falls within a Medicare benefit category (e.g., physicians' service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids).
   2. The trial must not be designed exclusively to test toxicity or disease pathophysiology. It must have therapeutic intent.
   3. Trials of therapeutic interventions must enroll patients with diagnosed disease rather than healthy volunteers. Trials of diagnostic interventions may enroll healthy patients in order to have a proper control group.

The three requirements above are insufficient by themselves to qualify a clinical trial for Medicare coverage of routine costs. Clinical trials also should have the following desirable characteristics; however, some trials, as described below, are presumed to meet these characteristics and are automatically qualified to receive Medicare coverage:

1. The principal purpose of the trial is to test whether the intervention potentially improves the participants' health outcomes;
2. The trial is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use;
3. The trial does not unjustifiably duplicate existing studies;
4. The trial design is appropriate to answer the research question being asked in the trial;
5. The trial is sponsored by a credible organization or individual capable of executing the proposed trial successfully;
6. The trial is in compliance with Federal regulations relating to the protection of human subjects; and
7. All aspects of the trial are conducted according to the appropriate standards of scientific integrity.

B. Qualification Process for Clinical Trials.Using the authority found in §1142 of the Act (cross-referenced in §1862(a)(1)(E) of the Act), the Agency for Healthcare Research and Quality (AHRQ) will convene a multi-agency Federal panel (the "panel") composed of representatives of the Department of Health and Human Services research agencies (National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), AHRQ, and the Office of Human Research Protection), and the research arms of the Department of Defense (DOD) and the Department of Veterans Affairs (VA) to develop qualifying criteria that will indicate a strong probability that a trial exhibits the desirable characteristics listed above. These criteria will be easily verifiable, and where possible, dichotomous. Trials that meet these qualifying criteria will receive Medicare coverage of their associated routine costs. This panel is not reviewing or approving individual trials. The multi-agency panel will meet periodically to review and evaluate the program and recommend any necessary refinements to HCFA.

Clinical trials that meet the qualifying criteria will receive Medicare coverage of routine costs after the trial's lead principal investigator certifies that the trial meets the criteria. This process will require the principal investigator to enroll the trial in a Medicare clinical trials registry, currently under development.

Some clinical trials are automatically qualified to receive Medicare coverage of their routine costs because they have been deemed by AHRQ, in consultation with the other agencies represented on the multi-agency panel to be highly likely to have the above-listed seven desirable characteristics of clinical trials. The principal investigators of these automatically qualified trials do not need to certify that the trials meet the qualifying criteria, but must enroll the trials in the Medicare clinical trials registry for administrative purposes, once the registry is established.

Effective September 19, 2000, clinical trials that are deemed to be automatically qualified are:

1. Trials funded by NIH, CDC, AHRQ, HCFA, DOD, and VA;
2. Trials supported by centers or cooperative groups that are funded by the NIH, CDC, AHRQ, HCFA, DOD and VA;
3. Trials conducted under an investigational new drug application (IND) reviewed by the FDA; and
4. Drug trials that are exempt from having an IND under 21 CFR 312.2(b)(1) will be deemed automatically qualified until the qualifying criteria are developed and the certification process is in place. At that time the principal investigators of these trials must certify that the trials meet the qualifying criteria in order to maintain Medicare coverage of routine costs. This certification process will only affect the future status of the trial and will not be used to retroactively change the earlier deemed status.

Medicare will cover the routine costs of qualifying trials that either have been deemed to be automatically qualified or have certified that they meet the qualifying criteria unless HCFA's Chief Clinical Officer subsequently finds that a clinical trial does not meet the qualifying criteria or jeopardizes the safety or welfare of Medicare beneficiaries.

Should HCFA find that a trial's principal investigator misrepresented that the trial met the necessary qualifying criteria in order to gain Medicare coverage of routine costs, Medicare coverage of the routine costs would be denied under §1862(a)(1)(E) of the Act. In the case of such a denial, the Medicare beneficiaries enrolled in the trial would not be held liable (i.e., would be held harmless from collection) for the costs consistent with the provisions of §§1879, 1842(l), or 1834(j)(4) of the Act, as applicable.Where appropriate, the billing providers would be held liable for the costs and fraud investigations of the billing providers and the trial's principal investigator may be pursued.

Medicare regulations require Medicare+Choice (M+C) organizations to follow HCFA's national coverage decisions. This NCD raises special issues that require some modification of most M+C organizations' rules governing provision of items and services in and out of network. The items and services covered under this NCD are inextricably linked to the clinical trials with which they are associated and cannot be covered outside of the context of those clinical trials. M+C organizations therefore must cover these services regardless of whether they are available through in-network providers. M+C organizations may have reporting requirements when enrollees participate in clinical trials, in order to track and coordinate their members' care, but cannot require prior authorization or approval.

Transmittal Number

126

Transmittal Link

http://www.cms.hhs.gov/transmittals/downloads/R126CIM.pdf

Revision History

09/2000-Implemented new policycovering routine costs in clinical trials. Effective and implementation dates 09/19/2000. (TN 126) (CR 1241)

Claims Processing Instructions

- TN AB-01-142 (Program Memorandum Intermediaries/Carriers)
- TN AB-01-103 (Program Memorandum Intermediaries/Carriers)
- TN AB-00-111 (Program Memorandum Intermediaries/Carriers)
- TN 131 (One Time Notification)
- TN 487 (Medicare Claims Processing Manual)

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[1] http://clinton4.nara.gov/WH/New/html/20000607.html

[2] Pub. L. No. 106-129, §2(b)(2), provided that any reference to the Administrator for Health Care Policy and Research is deemed to be a reference to the Director of the Agency for Healthcare Research and Quality.

[3] Public Law 103-43.

[4] *http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm*

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